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Apparatus and method for diagnostic gas analysis

The present invention relates to the field of diagnostic gas analysis, and in particular to the determination of endogenous nitric oxide (NO) in exhaled breath of humans.

Background of the invention

The discovery of endogenous NO in exhaled air, and its use as a diagnostic marker of inflammation dates back to the early 1990 (See e.g. WO 93/05709; WO 95/02181). Today, the significance of endogenous NO is widely recognised, and since a few years back, a clinical analyser is available on the market (NIOX®, the first tailor-made NO analyser for routine clinical use with asthma patients, AEROCRINE AB, Solna, Sweden).

In the summer of 1997 the European Respiratory Journal published guidelines (ERS Task Force Report 10:1683-1693) for the standardisation of NO measurements in order to allow their rapid introduction into clinical practice. Also the American Thoracic Society (ATS) have published guidelines for clinical NO measurements (American Thoracic Society, Medical Section of the American Lung Association: Recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide in adults and children - 1999, in Am J Respir Crit Care Med, 1999; 160:2104-2117).

The NIOX® analyser, and others intended for research applications, is based on chemiluminescence determination of NO. While highly accurate and reliable, chemiluminescence determination requires an advanced apparatus involving a vacuum pump, dehumidification of the exhaled air, to mention a few examples. Although the chemiluminescence analysers have

developed significantly, they are still rather expensive and bulky.

Prior art

WO 01/26547 discloses a handheld respiratory NO meter having a low resistance flow pathway throughout the device. Placed in this pathway is a NO concentration sensor generating electrical signals as a function of the instantaneous fraction of NO as the respiration gases pass through the flow pathway. The NO sensor is defined as a fluorescence based sensor having a response time preferably less than or equal to 200 ms, and most preferably less than or equal to 100 ms. Even faster response times are stated to be desirable.

While appealing as a concept, it appears to be practically very difficult if not impossible to achieve accurate and reliable NO determinations in the ppb range using the device of WO 01/26547.

The objective of the present invention is to make available a portable, preferably handheld device, for diagnostic determinations of NO. Further aims include the goal to make the device easy to use, robust and reliable, while maintaining the high accuracy and sensitivity of the chemiluminescence analysers.

One particular objective of the present invention is to make available a device for diagnostic NO-measurements operating with an electrochemical sensor, which device is easily used in the clinics or at point-of-care, however without compromising the accuracy and reliability of the measurements.

Another objective is to make available a handheld and robust device, preferably also being a relatively low-cost device, again without compromising the accuracy and reliability of the measurements.

Further objectives, solved by the present invention, and advantages associated therewith will become evident from the following description and examples.

Summary of the invention

The objectives of the present invention are met by a device and method according to the attached claims. According to the invention, the device comprises at least an electrochemical NO sensor, an inlet/outlet through which a patient inhales NO-free air through a scrubber, and exhales exhaled air at a predetermined flow rate and pressure, a buffer chamber for temporarily storing a portion of the exhaled air, and means for feeding said portion of the sample to said NO sensor at a flow rate much below the exhalation flow rate. The method includes at least the steps corresponding to the above.

Short description of the drawings

The invention will be described in closer detail in the following description, non-limiting examples, and claims, with reference to the attached drawings in which:

Fig. 1 shows schematically the components of a device according to the invention.

Description

The present inventors have surprisingly shown that the electrochemical sensor technology can be successfully applied in diagnostic measurements of NO. It was however not possible to apply an electrochemical sensor to NO measurements directly, as such sensors have considerably longer response times, e.g. as compared to chemiluminescence apparatuses, high sensitivity to contaminants, e.g. a cross sensitivity to water vapour, and a considerable temperature and flow dependence. In order to successfully apply the electrochemical sensor

technology to diagnostic NO measurements where a high reliability and accuracy in the ppb range is required, a novel device had to be developed.

In general terms, the device according to the invention has the following functionality and/or means for performing said functions (see also Fig. 1):

The device has a combined inlet/outlet 1, capable of engaging a disposable filter (not shown) through which the patient inhales NO-free air and exhales, during which exhalation phase a sample is taken for NO-measurement and led to the sensor.

Preferably the inlet of the device is designed to tightly engage a disposable patient filter. This filter may be a conventional filter, capable of ensuring viral/bacterial free air during normal inhalation. (Specifications?) The filter is preferably a XXXX filter, marketed by Aerocrine AB, Solna, Sweden (Catalogue no. XXXX).

The patient inhales clean, NO-free air through the filter, and then exhales through the same filter, into the device. The filter thus fills two functions, as it both protects the patient and the device from particulate matter, viruses, bacterial, aerosols etc. The disposable filter has the added advantage of preventing spread of infections or patient-to-patient contagion.

In the vicinity of the inlet/outlet 1, a pressure sensor 2 is situated. The pressure sensor has the function of monitoring the breath, to ensure that the soft palate is closed during exhalation, and to check that the inhalation of NO-free air is performed through the apparatus, i.e. through a NO-scrubber 3. The device also has an inlet 4 for ambient air, leading to said scrubber 3. The scrubber in turn is connected via an one-way valve 5 to the inlet/outlet 1, so that the patient can

inhale NO-free air, but preventing exhaled air to pass said one-way valve.

The scrubber may be a conventional chemical NO scrubber, having an inlet and an outlet, and a main body filled with suitable filter media, e.g. a $KMnO_4$ based filter media, such as Purafil® Select (Purafil Inc., USA) in a custom filter supplied by AirSafety Ltd. The construction of the filter, and arrangements for taking a zero sample form the subject of a co-pending patent application.

Further, in connection to the inlet/outlet 1 is a flow regulator 6, which has the function of controlling the exhalation flow to 50 ml (± 5 ml/s) when the user adapts to the feedback given by the device. ***KAN VI ANGE ETT BREDARE INTERVALL FÖRST; OCH SEDAN DETTA SOM EN FÖREDRAGEN UTFÖRINGSFORM? VILKET ÄR DET BREDARE INTERVALLET?***

The exhalation air is then led, through the flow regulator 6, to a buffer chamber 7, at the end of which a flush valve 8, and a three-way valve 9, are situated. During the initial phase of the exhalation, the flush valve 8 is open, and the three-way valve 9 closed, and the exhaled air is thus led to the ambient atmosphere. At a predetermined time, the flush valve 8 will close, and the three-way valve 9 open, so that the sample stored in the buffer chamber 7 will be led though the three-way valve 9, with the aid of a sample pump or fan 10, to the sensor 11.

According to a preferred embodiment of the invention, the sample pump 10 is a plunger pump. This type of pump has the advantages of being insensitive to variations in flow, and gives a low, even flow with high accuracy.

Before reaching the sensor, the sample is preferably led through means 12 for equalising the humidity of the sample to

ambient conditions, and means 13 for equalising the temperature of the sample to that of the sensor.

Preferably said means 13 acts to temperate both the sample and the sensor, e.g. by surrounding the sensor and by forming a large contact area for the gas flow. Alternatively, the temperature of the sample and/or that of the sensor is measured, and the results compensated for the temperature according to the specifications of the sensor.

The device further comprises means for controlling the functions of the above means, such as control electronics 14, which receive and analyse input e.g. from the sensors, and the user interface, and control the valves and the sample pump. The means 14 will also handle data acquisition, signal processing, data storage, communication with external units, and the user interface. External communication can be performed using one or several of the following options: a memory card or microprocessor card, an EEPROM card, in the following designated "smartcard", IR-communication or via a conventional serial or parallel port.

The provision of a smartcard has the among other advantages, the particular advantage that every patient is free to use any device according to the invention, and information relating to the patient will automatically be stored in the device, together with the measurement results. Simultaneously, information relating to the device and sensor, will automatically be stored on the smartcard, together with the measurement results. This gives greatly added flexibility, without compromising the documentation requirements in diagnostic applications.

The device further comprises a user interface 15, one component of which has the form of a display, such as a liquid crystal display (LCD), preferably a touch screen, for

displaying data to the user, and for receiving commands and settings from the user, e.g. for programming and/or parameter setting, functionality check or similar, performed by a qualified user, or by specifically designated service staff. Alternatively, these functions or part thereof may be performed through a conventional PC-interface, e.g. a conventional serial port, a parallel port or an USB port.

The device preferably also comprises means for keeping track of current date and time, as well as means for setting the current date and time. There is preferably also an alarm function, which can be set for single or recurrent alarms, for example a specific time every day. It is possible to set the alarm time and recurrence, as well as to enable / disable the alarm. The alarm function has the advantage of improving patient compliancy with regard to monitoring their condition, and hopefully also with regard to the treatment of the same.

In summary, the input reaching the means 14 consist of signals from the pressure sensor, the NO sensor, the user interface, and the temperature control. The output leaving the means 14 consist of signals regulating the position of the flush valve, the three-way valve, the sample pump, the temperature control and the user interface.

An electrochemical sensor has a considerably longer response time than other, hitherto used NO sensors, such as the commonly used chemiluminescence sensors. While a chemiluminescence sensor makes an instantaneous determination of the NO concentration in a gaseous sample, an electrochemical sensor requires longer time for establishing a stable signal. If correctly calibrated, chemiluminescence sensors are also highly accurate, down to a ppb level. Consequently electrochemical sensors have hitherto not been

used for diagnostic NO measurements, i.a. due to their long response time, and their relatively high detection levels.

In the device according to the invention, the sample of exhalation air is temporarily stored in a buffer chamber, which makes it possible to expose the sensor to a zero-sample or a patient sample at a steady flow, during a prolonged period of time, in order to obtain an accurate response from the sensor.

The device according to the invention includes a buffer chamber, and means for filling said buffer chamber with a sample of NO-free air for zero-point adjustment, and during controlled exhalation, a sample of exhaled air for NO measurement. The means for filling said buffer chamber with NO-free air is preferably a sample pump or fan, drawing air through a NO-scrubber. The means for filling said buffer chamber with a sample of exhaled air is preferably a valve allowing exhaled air to fill the buffer chamber during a pre-set duration of the exhalation.

When the buffer chamber is filled with the desired sample, means for delivering the sample to the sensor is/are activated. Such means include a sample pump or fan, supplying the sensor with a flow of about 2 ml/s during a predetermined time, preferably about 50 s. ***KAN VI HÄR OCKSÅ ANGE ETT BREDARE INTERVALL FÖRST; I SÅ FALL VILKET?***

The buffer chamber is a space for temporarily storing a portion of exhaled breath, in order to deliver it to the sensor at a flow and during a duration of time, adapted to the response time of said sensor. Preferably said buffer chamber is a space which meets the following requirements:

- no significant diffusion of NO into the walls of the buffer chamber

- no significant diffusion of substances which interfere with the NO measurement
- turbulent flow
- no significant adhesion of NO to the walls

According to one embodiment of the invention, said buffer chamber is formed as a maze of canals with a square or rectangular cross section, e.g. moulded in a block of thermoplastic material, preferably polypropylene.

According to another embodiment, said buffer chamber is formed as a length of tubing of a suitable, inert material, such as silicone tubing.

According to yet another embodiment, said buffer chamber is formed as a cylinder with a movable end wall or piston. By operating said end wall or piston longitudinally, sample is aspirated into and displaced out from the cylinder. This embodiment can be exemplified by a syringe where the volume of the syringe corresponds to the volume of the sample to be taken, and the rate at which the piston displaces the sample is equal to the rate at which the sample is to be fed to the sensor.

According to yet another embodiment, said buffer chamber is formed as a bellows of a suitable material. The sample is allowed to enter the bellows, either by the pressure exerted by the patient when exhaling into the device, or aided by mechanically expanding the bellows. The sample is then displaced by mechanically compressing the bellows.

In the determination of nitric oxide concentration using an electrochemical sensor, both the temperature of the sensor and the gas flow are critical factors. The temperature of the sensor influences its sensitivity, and consequently

fluctuating temperatures between separate measurements will result in poor repeatability and reduced accuracy. Correspondingly, the temperature of the gas flow, as it meets the surface of the sensor, will influence the temperature of the sensor, with the above consequences.

In the device according to the present invention, and in the corresponding method, the temperature may be registered, and the results adjusted to the temperature using a correlation factor. Preferably, the temperature of both the gas and the sensor is accurately controlled by enclosing the sensor in means which both temperate the sensor and the sample gas before it reaches the sensor. The construction of such means is the subject of a co-pending patent application.

Electrochemical sensors are known to be sensitive to fluctuations in humidity, and it is also possible that the sensor cross reacts with water vapour. The device according to the invention preferably includes means for equalising the humidity of the sampled exhalation air, as well as the zero sample, with ambient humidity. Such means may consist of a Nafion® tube, through which the sample is led (Nafion® is a perfluorinated polymer membrane, marketed by E.I. du Pont de Nemours & Co). The advantage of this lies in that the patient sample and the zero sample will have the same humidity when reaching the sensor.

Electrochemical sensors unfortunately have a limited life span, due to ... ***En kortfattad teknisk förklaring vore på sin plats...***

According to the method and device of the present invention, the life span of the sensor is subject of a two-fold consideration. The device is equipped with means capable of establishing the production date and/or calibration date and/or expiration date of th sensor, e.g. by reading such

information stored in association to the sensor, preventing use of the sensor according to pre-set crit ria, e.g. when the expiration date is reached.

The device is further equipped with means for registering the number of measurements performed with a sensor, and preventing use of the sensor according to pre-set criteria, e.g. when the maximum number of measurements for an individual sensor is reached.

The above means and associated functions have the advantage of making it possible to guarantee that each measurement is performed with a well functioning sensor.

The device according to the present invention has a novel, greatly simplified visual interface. The visual interface comprises a display, which indicates the state of the device (e.g. ON / START UP / READY / BUSY / OFF etc.) and guides the user through the inhalation and/or exhalation, and presents the result of the measurement. This display is preferably a conventional display, such as a liquid crystal display (LCD). Most preferably said display is a so called touch screen.

The above functions can be further supported by visual and audible signals, such as one or more blinking light/-s, lights of different colours, an audible signal which changes in tone or rhythm, all depending on the state of the device, or on the performance of the patient when inhaling and/or exhaling. For example, the device may display one colour when in START UP mode, and another colour when the START UP mode is completed, and the device is ready for measurements or enters READY mode. Likewise, the device may display one first colour, either blinking or steady, when the user inhales and/or exhales incorrectly, and another second colour or other signal, clearly distinguishable from said first colour or signal when the inhalation and/or exhalation is performed according to

pre-set requirements, ensuring good repeatability of the measurements. Parameters to be controlled and associated to visual and/or audible signals include the duration and flow of the inhalation, and the exhalation, respectively.

The above means and associated functionalities makes the device suitable for use by all patients, either alone or under the supervision of medical personnel, e.g. their treating physician or nurse, for point-of-care use, as well as for home use by individual patients, monitoring their disease.

The device according to the present invention is preferably capable of communicating with its surroundings in many ways. With the patient, the device will communicate audibly and/or visually, indicating basic functions, state of readiness, proper use (inhalation, exhalation) and the result of the measurement. It is possible e.g. to send configuration data between a smartcard (via the device) and external software.

Further, the device preferably includes an IR port for communication with a stationary computer, e.g. for storing patient data in a data base, for further analysis of the data etc. The IR port may also work to incorporate the device in a local network, enabling the use of local printers or in other ways to handle measurement results and patient information.

The device according to the invention preferably also includes a smartcard interface for entering and storing individual patient data. When using the device, each user would be given a personal smartcard. Preferably the smartcards would be pre-programmed to contain the settings relevant for different patient groups, e.g. male, female, child, or the settings relevant to patients of different age or bodyweight, in order to account for differences in dead space, or other physiologic differences.

The NO measurement results would then be recorded on the smartcard, together with information regarding the identity of the device and sensor used in the measurement, the date and time of the measurement, and optionally the ambient temperature and humidity. According to one embodiment, the smartcard would be designed to carry the patient history, and NO levels, optionally together with information regarding medication, doses, and subjective information, such the state of health, assessed by the patient or by the treating physician or nurse.

The device is preferably also capable of communicating with external software, installed on an external computer, such as a PC. It is then possible e.g. to send measurements from a smartcard (via the inventive device) to said external software.

According to one embodiment, it is also possible to send measurements from the internal memory of the device to external software.

Likewise, according to another embodiment, it is also possible to download software updates to the inventive device from external software.

It is preferably further possible to send an error log from the inventive device to external software.

The device according to the present invention may further include an AC/DC converter, preferably an external converted feeding the device with DC 12 V. The device further contains a rechargeable battery, and a power unit supplying the required voltage to the components of the device. A battery for memory and sensor charging back-up is also included.

The device according to the invention preferably comprises an internal memory, preferably with the possibility to store data

from at least 2000 measurements. Alternatively, or in addition to the internal memory, the device will be capable of recording information on a removable data medium, such as a so called smartcard, a memory card, a microprocessor card, an EEPROM, a mini disc, diskette, or the like. The data to be recorded in the internal memory and/or on a smartcard or similar may comprise:

- date and time of measurement
- measured FE_{NO}
- sensor ID No.
- device ID No.
- up to 7 asthma and 1 comfort inputs in advanced mode
- up to 5 medication inputs in advanced mode

Optionally, when measurement data memory is full, the oldest data is overwritten with new data.

Preferably also a minimal error list is provided either in the internal memory, or on the smartcard, or in duplicate on both of these, consisting of at least the following entries:

- error number
- timestamp

According to a preferred embodiment, patient configuration is stored on the smartcard. The patient information may be general information, relating to different patient groups, such as male/female, child/adult/elderly, and further information, if diagnostically relevant. Preferably the smartcards are colour coded, each colour corresponding to one patient group. Preferably the smartcards are printed with a clearly visible number or code, so that individual cards can be distinguished. Preferably the smartcards have an area where the name of the patient can be printed or hand-written.

The patient information may also be individual information, relating to a specific patient. In both cases, the information may comprise:

- recommended max FE_{NO} value
- recommended min FE_{NO} value
- one mode of 'Adult', 'Child' or 'Small child'
- TBD ***Vad är detta?***

The internal memory of the device according to the invention is preferably able to store both NO measurements and user input, including input e.g. by manufacturer and maintenance personnel. For example, the device is able to store errors to said internal memory.

The device is preferably also able to store configuration parameters to the internal memory, such as:

- production date
- calibration date
- sensor input calibration

The device is preferably also able to store settings parameters to the internal memory, such as:

- top LED intensity
- volume
- contrast
- alarm time
- current time and date

According to a preferred embodiment, the electrochemical NO sensor is integrated to a circuit comprising a memory, in the following called "sensor memory". This is preferably a memory circuit of EEPROM-type. Said sensor memory is capable of communicating and/or interacting with the internal memory and control circuits of the device.

In other words, it will be possible to read data from the sensor memory, such as:

- sensor calibration data
- expiration date
- total number of measurements on sensor
- remaining number of measurements on sensor

It is also possible to decrease remaining number of measurements on sensor at the rate at which measurements are performed.

According to a preferred embodiment, the inventive device will be capable of indicating when the expiration date of the sensor is approaching, or when the remaining number of measurements reaches a predetermined low value, and alerting the user. When the expiration date is reached, or when the number of measurements exhausted, the device will block further use of the sensor and alert the user.

According to the invention, the device keeps track of current time and date. It will also be possible to set current time and date, and current time and date is retained during backup battery operation.

There are numerous advantages related to the provision of a sensor memory. One is safety, as the expiration date will be automatically checked, and the use of the sensor automatically blocked when this date is passed. Another safety issue is the automatic control of the number of measurement, where the use of the sensor is automatically blocked when a maximum number of measurements is reached.

Example

FE_{NO} Measurement

In the method according to the invention, before a measurement is started, the following conditions must be fulfilled:

A) a valid sensor is be inserted:
- relevant checksums correct.
- sensor production date earlier than current date
- sensor expiration date later than current date
- sensor measurements remaining

B) a valid smartcard is be inserted:
- relevant checksums correct
- smartcard is of patient type.

C) all supervised parameters (temperature, ***) are in range as defined below.

D) the user makes a request to measure through the user interface.

E) if any of the conditions A) through C) is not fulfilled, the user will be informed and measurements prohibited.

The NO measurement and thereby also the method comprises the following steps: inhalation, exhalation, breath stabilization, breath measure, zero stabilization and zero measure phases in mentioned order.

Preferably, the measurement process time is be less than 3 minutes.

The inhalation phase will start when a pressure below value set in internal configuration memory is detected.

According to an embodiment, if the device is in "small child mode" governed by smartcard settings or input from the user, the inhalation phase will be bypassed.

The exhalation phase will start when a pressure above value set in internal configuration memory is detected.

According to an embodiment, if the device is in "adult mode", then breath stabilization phase will start after 10s exhalation. Otherwise breath stabilization phase will start after 6 s exhalation.

Breath measure phase will start after breath stabilization time set in the internal configuration memory, and signal mean is calculated for the breath measure phase. Also signal noise and signal slope are calculated for the breath measure phase.

The zero stabilization phase starts after a breath measure time set in internal configuration memory. Following this, the zero measure phase starts after a zero stabilization time set in the internal configuration memory. As above, signal mean, signal noise, and signal slope are calculated for the zero measure phase.

The process is finished after zero measure time set in internal configuration memory. The pump 10 will be on during the entire process.

The flush valve 8 will be open during exhalation phase, otherwise it will be closed.

The 3/2-valve 9 will select breath gas during the exhalation, breath stabilization and breath measure phases, otherwise it will select zero gas.

If any of the supervised parameters does not remain within range as defined below an error message will be issued.

Result

The result of the measurement is calculated as the difference between the mean values of exhaled breath and zero gas. The result is then multiplied by a calibration constant to get

sensor output value. The result is further multiplied by a sensor calibration constant to get ppb value.

For the result to be considered valid, the following conditions must be fulfilled:

- noise for exhaled breath less than limit set in internal configuration memory
- noise for zero gas less than limit set in internal configuration memory
- slope absolute value for exhaled breath less than limit set in internal configuration memory
- slope absolute value for zero gas less than limit set in internal configuration memory
- mean level of exhaled breath may not be within 10% of ADC saturation limits
- mean level of NO-free gas may not be within 10% of ADC saturation limits
- result must not be less than 0 ppb. (note: system requirement states 5 ppb which gives us room for noise)

*** Skall denna not vara med???***

If a result turns out to be negative, the stored result will be 0 ppb.

After a completed measurement, the sensor measurements counter is decreased by one, and the result stored to the internal memory. Optionally, the result is stored on a smartcard. Further, the result will only be presented to user if valid. If the result is not valid, an error message will be issued.

Ambient measurement

The ambient measurement process consists of ambient stabilization, ambient measure, zero stabilization and zero measure phases in mentioned order.

The ambient stabilization phase starts at request by the user, and following such request, the ambient measure phase starts after ambient stabilization time set in internal configuration memory.

Signal mean, signal noise, and signal slope are calculated for the ambient measure phase.

The zero stabilization phase will start after the ambient measure time set in internal configuration memory. Zero measure phase starts after zero stabilization time set in internal configuration memory.

Signal mean, signal noise, and signal slope are calculated for zero measure phase.

The process is finished after zero measure time set in internal configuration memory. The pump 10 is on during the entire process. The flush valve 8 is closed during the entire process, while the 3/2-valve 9 will select breath/ambient gas during ambient stabilization and ambient measure phases, otherwise it will select zero gas.

If any of the supervised parameters does not remain within range as defined below an error message will be issued.

Result

The result of the measurement is calculated as the difference between the mean values of ambient and zero gas. The result is then be multiplied by a calibration constant to get sensor output value. The result is further multiplied by a sensor calibration constant to get ppb value.

For the result to be considered valid, the following conditions must be fulfilled:

- noise for ambient air less than limit set in internal

configuration memory
- noise for zero gas less than limit set in internal configuration memory
- slope absolute value for ambient air less than limit set in internal configuration memory
- slope absolute value for zero gas less than limit set in internal configuration memory
- mean level of ambient air may not be within 10% of ADC saturation limits
- mean level of NO-free gas may not be within 10% of ADC saturation limits
- result must not be less than 0 ppb.

If the result is negative, the stored result will be 0 ppb. Further, the result will only be presented to user if valid, and if the result is not valid, an error message will be issued.

Control

Temperature

In this example, the means for temperature control consist of a Peltier element. The sensor temperature is kept at value set in internal configuration memory: If the measured temperature is below 16°C, the element will be off. ***SKALL DET INTE VARA "ON"?*** If the measured temperature is above 35°C, the element will be off.

The temperature will be considered invalid if it has been outside configured sensor temperature ± 1°C during the last 5 minutes. If the temperature is invalid for more than 30 minutes an error message is issued.

Pump

The pump 10 is actively controlled during measurement process. Otherwise the pump will be off.

3 way valve

The valve 9 is actively controlled during measurement process. Otherwise the valve will be in released state.

2 way valve

The valve is actively controlled during measurement process. Otherwise the valve will be in released state.

Pressure

Pressure is always measured relative ambient pressure. Ambient pressure is defined as the pressure when user requests a measurement. During the first 1 second of inhalation, the pressure is required to remain below a value set in the internal configuration memory. During the exhalation phase, except for the first 3 seconds, the pressure is further required to remain within max and min values set in the internal configuration memory. During the exhalation phase, a warning will be issued if the pressure is not within high and low values set in the internal configuration memory. During the processing phase, after a transition time of 2 seconds, the pressure is required to remain within ± 1 cmH_2O.

Smartcard

The smartcard is inserted by the used when activating the device or before a measurement is performed, and is to remain inserted during the entire measurement process. If there is less than 10% free m asurement storage capacity on said smartcard, the user will be notified before measurement.

Power

When the external power is removed, the processor enters low power sleep mode. When external power is applied, the processor exits low power sleep mode. The start up time after external power is applied is preferably less than 2 minutes.

Self test

The following functionalities are tested each time external power is applied:

- Correct application firmware checksum
- Main board memory responding
- TBD add more here ***VAD VILL NI LÄGGA TILL?***

If self test fails an error message will be issued.

Exception handling

Errors are always logged to database on main board memory. If a patient smartcard is inserted when an error occurs, the error will be logged to smartcard.

Importantly, the user will be notified when an error occurs.

The device and method according to the present invention offers many advantages. Numerous sources of error are avoided, or minimized.

For example, as the device registers the negative pressure when a patient inhales through the device, and thus through the NO scrubber supplying NO free air, the correct performance of the inhalation is controlled. The pressure check is further supplemented by feedback, guiding the patient to perform a correct inhalation, or informing the patient when the inhalation was correct, and when it was insufficient.

The device and method further have built-in means and functions or operations, which constantly ensure that the electrochemical sensor functions properly.

Although the invention has been described with regard to its preferred embodiments, which constitute the best mode presently known to the inventors, it should be understood that various changes and modifications as would be obvious to one having the ordinary skill in this art may be made without departing from the scope of the invention as set forth in the claims appended hereto.

Claims

1. Device for diagnostic NO measurements, **characterized** in that said device comprises an electrochemical NO sensor (11), an inlet (1) through which a patient exhales at a predetermined flow rate and pressure, a buffer chamber (7) for temporarily storing a portion of the exhaled air, and means (10) for feeding said portion of the sample to said NO sensor at a flow rate much below the exhalation flow rate.

2. Device according to claim 1, wherein the device comprises a flow regulator (6) for controlling the exhalation flow.

3. Device according to claim 1, wherein the means (10) for feeding said portion of the sample to said NO sensor operates to create a steady flow of about 2 ml/s during at least about 30 s.

4. Device according to claim 1, wherein the device comprises means (12) for equalizing the humidity of the sample.

5. Device according to claim 4, wherein said means for equalizing the humidity of the sample consist of a length of tube, made from a catalytic membrane material.

6. Device according to claim 1, wherein the device comprises means for controlling the parameters of the inhalation and exhalation.

7. Device according to claim 6, wherein said means comprises a pressure sensor (2) and means for giving feedback to the patient.

8. Device according to claim 1, wherein the buffer chamber (7) is a maze.

9. Device according to claim 1, wherein the buffer chamber (7) consists of a cylinder with a movable piston.

10. Device according to claim 1, wherein the buffer chamber (7) consists of a length of tube.

11. Device according to claim 1, wherein the device comprises a NO-scrubber through which a patient inhales directly prior to exhaling into the device, thus ensuring that the lungs of the patient are filled with NO-free air.

12. Device according to claim 1, wherein the device further comprises an interface for receiving a smartcard on which data linked to a specific user can be stored, and onto which measurement data can be recorded.

13. Device according to claim 12, wherein the device is capable of adapting to different users or different user groups, based on the data stored on the smartcard.

14. A smartcard carrying data concerning an individual patient or patient group, wherein at least the following data are recorded on said smartcard

- date and time of measurement
- measured FE_{NO}
- sensor ID No
- device ID No

15. Method for diagnostic NO measurements using a device comprising an electrochemical NO sensor, **characterized** in that:

- a patient exhales into said device,
- the flow rate and pressure is controlled to a preset value, respectively,

- a sample of the exhalation air is temporarily stored in a buffer chamber,

- said sample is fed to said electrochemical NO sensor at a flow rate much lower than the exhalation flow rate, and

- the NO concentration is determined in said sample.

16. Method according to claim 15, wherein the patient inhales NO-free air prior to exhaling into the device.

17. Method according to claim 15, wherein the patient inhales through a NO-scrubber integrated in said device, supplying NO-free air to the patient, prior to exhaling into the device.

18. Method according to claim 15, wherein the patient is given audible or visual feedback during the inhalation and exhalation steps, in order to support the correct performance of said steps.

19. Method according to claim 15, wherein the exhalation flow rate is controlled to a value of about 50 ml/s and the rate at which the sample is fed to the sensor is about 2 ml/s. ***INTERVALL?***

20. A method according to any one of claims 15 - 19, wherein at least one of the following steps is included:

- the patient enters information relating to his/her intake of a medicament

- the patient subjectively assesses his/her state of health and enters corresponding information

21. A computer program comprising the instructions for performing the method according to any one of the claims 15 through 20.

22. A computer program according to claim 21, when stored on a medium.

Abstract

A handheld, small but accurate and reliable device for diagnostic NO measurements using an electrochemical NO sensor can be constructed if special technical considerations are taken. By temporarily storing a portion of the exhaled air, and feeding this to the sensor at a flow rate much lower than the exhalation flow rate, the accuracy and sensitivity of the electrochemical sensor is increased. The method for diagnostic NO measurements using electrochemical NO sensor comprises steps for controlling the inhalation of NO free air, as well as the exhalation, both by built-in means and by audible and/or visual feedback to the patient.

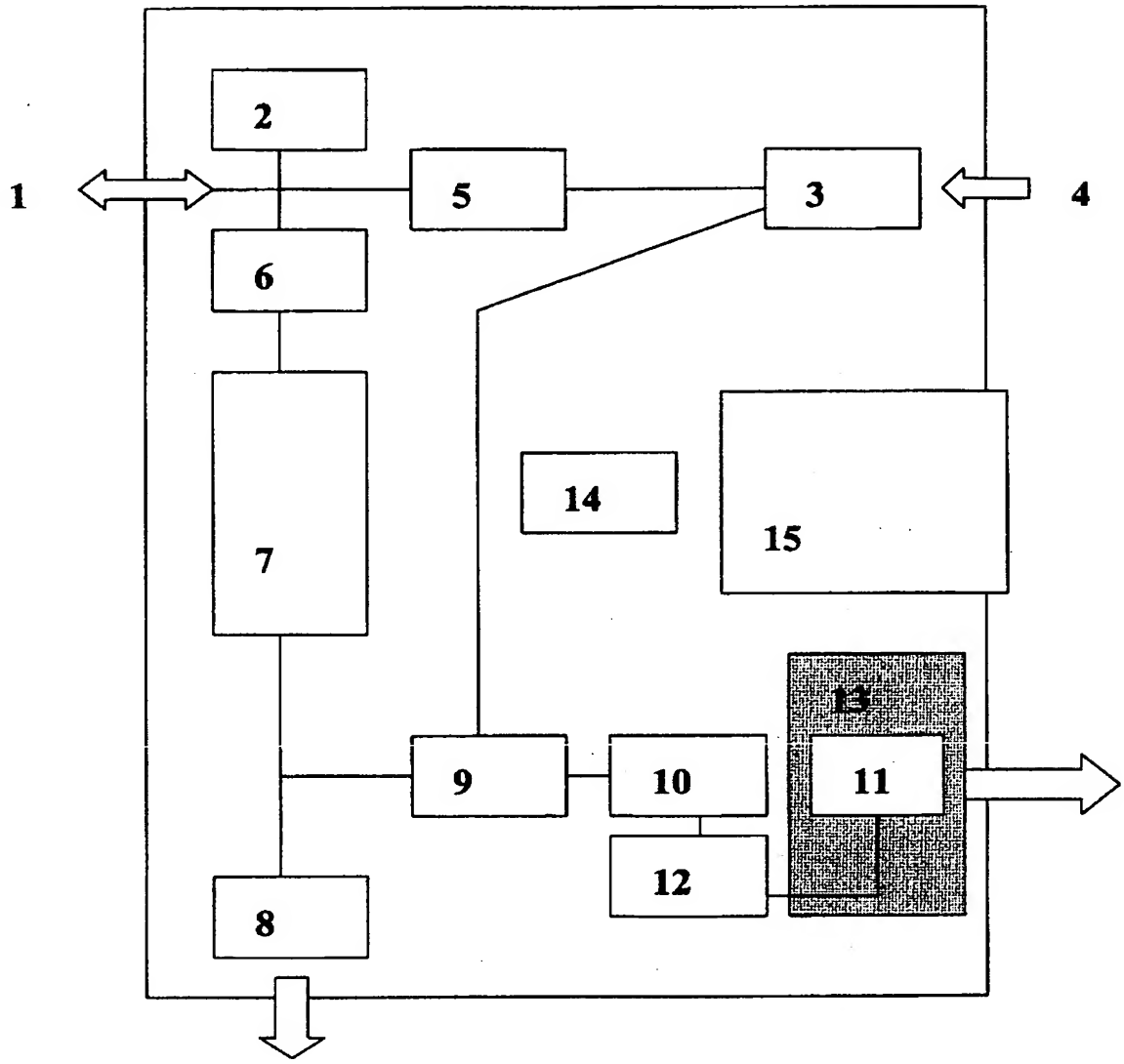

Fig. 1